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## LONGITUDINAL ANALYSES OF PRENATAL AND POSTNATAL LEAD EXPOSURE AND EARLY COGNITIVE DEVELOPMENT

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**Abstract** In a prospective cohort study of 249 children from birth to two years of age, we assessed the relation between prenatal and postnatal lead exposure and early cognitive development. On the basis of lead levels in umbilical-cord blood, children were assigned to one of three prenatal-exposure groups: low ( $<3 \mu\text{g}$  per deciliter), medium (6 to  $7 \mu\text{g}$  per deciliter), or high ( $\geq 10 \mu\text{g}$  per deciliter). Development was assessed semiannually, beginning at the age of six months, with use of the Mental Development Index of the Bayley Scales of Infant Development (mean  $\pm$  SD,  $100 \pm 16$ ). Capillary-blood samples obtained at the same times provided measures of postnatal lead exposure.

Regression methods for longitudinal data were used to evaluate the association between infants' lead levels and

their development scores after adjustment for potential confounders. At all ages, infants in the high-prenatal-exposure group scored lower than infants in the other two groups. The estimated difference between the overall performance of the low-exposure and high-exposure groups was 4.8 points (95 percent confidence interval, 2.3 to 7.3). Between the medium- and high-exposure groups, the estimated difference was 3.8 points (95 percent confidence interval, 1.3 to 6.3). Scores were not related to infants' postnatal blood lead levels.

It appears that the fetus may be adversely affected at blood lead concentrations well below  $25 \mu\text{g}$  per deciliter, the level currently defined by the Centers for Disease Control as the highest acceptable level for young children. (N Engl J Med 1987; 316:1037-43.)

**I**N a national survey conducted in the late 1970s,<sup>1</sup> 40 percent of U.S. children under five years of age had blood lead levels above  $20 \mu\text{g}$  per deciliter. Among city-dwelling black children, the figure approached 60 percent. A variety of enzymatic and neurophysiologic processes are impaired at this concentration.<sup>2-6</sup> Debate persists, however, regarding the blood lead level at which deficits in children's learning and behavior become apparent.<sup>7,8</sup> Limitations inherent in retrospective study designs may account for some of the controversy.<sup>9</sup> Detailed histories of children's exposure to lead and their development are rarely available, but both are necessary to determine whether lead exposure precedes or follows the appearance of a developmental deficit. Elevated lead exposure may be a marker of a preexisting handicap rather than its cause, resulting from the tendency of impaired children to have pica.<sup>10</sup>

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Some investigators have attempted to determine a child's cumulative exposure by measuring the lead content of shed deciduous teeth.<sup>11-14</sup> The usefulness of this tissue as a basis for reconstructing the details of exposure history has not been established, however. At present, there is no satisfactory way to obtain an adequate developmental history retrospectively.

Some of the methodologic limitations of retrospective studies can be avoided with a longitudinal design in which both children's lead exposure and their development are periodically measured, starting at birth. This design allows investigators to measure the temporal relations between changes in lead exposure and changes in behavior. Besides suggesting which of the competing causal models accounts best for the data, a longitudinal design permits assessment of various exposure variables (e.g., dose, timing, and duration). Few studies in humans have addressed such issues as the threshold for lead's developmental toxicity, the age or ages at which children are most vulnerable, and the relative effects of long-term and short-term exposures.

Using a longitudinal design, we obtained repeated measures of blood lead levels, development, and the correlates of both in a group of urban children followed from birth to the age of two years. Lead levels in umbilical-cord blood between 10 and  $25 \mu\text{g}$  per deciliter were associated with worse performance on tests of

infant development administered at six-month intervals through the second year of life.

## METHODS

### Sample Selection

Between April 1979 and April 1981, umbilical-cord blood samples were collected from the placentas of 11,837 babies born at the Brigham and Women's Hospital in Boston. The mean ( $\pm$ SD) lead concentration was  $6.6 \pm 3.2$   $\mu$ g per deciliter (range, 0 to 37).<sup>15</sup> In recruiting our longitudinal sample from this population, our goal was to select three groups of infants defined by their position within the distribution of values: below the 10th percentile (low), at approximately the 50th percentile (middle, or medium exposure), and above the 90th percentile (high). On the basis of the cord-blood lead concentrations of the infants born between April and July 1979 (approximately 2500), the criteria for eligibility in the three exposure groups were established at  $<3$   $\mu$ g per deciliter, 6 to 7  $\mu$ g per deciliter, and  $\geq 10$   $\mu$ g per deciliter, respectively. (At the beginning of the study, only infants with lead levels  $>15$   $\mu$ g per deciliter were eligible for the high-exposure group. A 20 percent decline in the mean cord-blood lead level over the period of sample collection,<sup>15</sup> as well as different degrees of success in enrolling infants in the three exposure groups, led us to modify the eligibility criteria over the course of the study.<sup>16</sup>) We obtained umbilical-cord blood samples for 9489 infants born during the subsequent 21 months (August 1979 to April 1981), representing 97 percent of the available population. Those with a blood lead level in one of the three target ranges were provisionally eligible for enrollment ( $n = 1207$ ). To be included in the study, infants also had to satisfy the following criteria: (1) absence of a medical condition considered to be a risk factor for developmental difficulty (e.g., Down's syndrome, cleft palate, gestational age  $<34$  weeks, and retinoblastoma); (2) birth into an English-speaking family; (3) residence near the Children's Hospital ( $<19$  km) in an area considered safe for home visitors, and (4) maternal consent to be contacted. Families meeting these criteria were sent letters introducing the study and then telephoned to request their participation. Those reporting an intention to move from our catchment area in the immediate future were excluded. Some families refused our request, and others could not be contacted by either letter or telephone. The final sample consisted of 249 families (Table 1). No infant in the longitudinal sample had a lead

level exceeding 25  $\mu$ g per deciliter, which is the current definition of an "elevated" blood lead level.<sup>17</sup> Two thirds of the infants in the high-lead group (50 of 76) had cord-blood lead levels between 10 and 15  $\mu$ g per deciliter.

### Sample Characteristics

The mean socioeconomic standing of the families contrasted sharply with that of families typically enrolled in research on the effects of lead exposure.<sup>18-20</sup> In general, the infants were healthy products of unremarkable pregnancies, with few of the characteristics of infants at increased risk of developmental handicap. Overall, 77 percent of the fathers and 70 percent of the mothers employed outside the home at the time of conception were in the top two social strata according to Hollingshead's index (combining occupational and educational achievement). Eighty-seven percent of the families were white, and 92 percent were intact. The differences in these and most other variables among the families with infants in the three cord-blood lead groups were slight and generally not in the direction expected on the basis of studies of the social correlates of childhood lead exposure<sup>21</sup> (Table 2). Infants with lead levels between 10 and 15  $\mu$ g per deciliter were compared for this same set of variables with infants with levels above 15  $\mu$ g per deciliter. The results were consistent with those in which all three exposure groups were compared, suggesting that infants already at higher risk of poor outcome for other reasons did not tend to have higher blood lead levels. Through our choice of delivery population and eligibility criteria, we were able to dissociate increased lead exposure from other risk factors. A more comprehensive comparison of the groups has been presented elsewhere.<sup>16</sup>

### Collection of Developmental Data

Infants and their families were contacted five times after delivery, when the infants were 1, 6, 12, 18, and 24 months of age (SD  $<2$  weeks at all ages). The assessment protocols at each age have been described elsewhere.<sup>22</sup> The principal outcome measures — the Bayley Scales of Infant Development<sup>23</sup> — were administered at all ages except one month. This assessment yields two scores: the Mental Development Index and the Psychomotor Development Index. In this report, we present longitudinal analyses of the infants' scores on the Mental Development Index, an age-corrected scale (mean  $\pm$ SD,  $100 \pm 16$ ) that assesses infants' "sensory-perceptual acuity, discriminations, and the ability to respond to these; the early acquisition of 'object constancy,' memory, learning, and problem solving ability; vocalizations and the beginnings of verbal communication; and early evidence of the ability to form generalizations and classifications, which is the basis of abstract thinking."<sup>23</sup>

Five examiners blinded to the infants' lead levels administered the Bayley scales. Interexaminer reliability was assessed separately for each age at which the scales were administered. The mean correlation between the Mental Development Index scores assigned by two examiners observing a third administer the scales exceeded 0.95 at all ages.

### Collection and Analysis of Blood Samples

Samples of umbilical-cord blood were collected at the time of delivery and analyzed according to procedures that have previously been described.<sup>15</sup> Specimens were sonicated and acid-digested in a microwave oven. The lead content was measured in duplicate by anodic stripping voltammetry (Environmental Sciences Associates [ESA] Model 2014, Bedford, Mass.).

Capillary blood samples, collected at 6, 12, 18, and 24 months, were assayed in duplicate or triplicate with an ESA Model 3010 anodic stripping voltammeter with use of an exchange reagent. The average difference between duplicate assays was 1  $\mu$ g per deciliter, and there was a difference of 3.5 or more in 10 percent of the pairs. The analytic systems were calibrated with aqueous standards of known lead concentrations. No interference from varying copper concentrations was observed. Each batch of samples was accompanied by blood samples of known lead concentration so that intra-laboratory variability could be quantified. In addition, several standardized blood samples, with lead concentrations measured to

Table 1. Reasons for Excluding Infants Whose Lead Levels in Umbilical-Cord Blood Were in One of the Target Ranges.

	LEAD LEVEL IN UMBILICAL-CORD BLOOD			TOTAL
	LOW	MEDIUM	HIGH	
No. of infants provisionally eligible	434	380	393	1207
No. excluded	349	292	317	958
Reason for exclusion*				
Lack of maternal consent	69	64	63	196
Birth complication†	17	17	4	38
Family not English-speaking	23	18	24	65
Location of residence‡	150	107	108	365
Refusal§	52	54	61	167
Moving	20	12	10	42
Unreachable	18	20	47	85
No. enrolled	85	88	76	249

\*Some infants were not acceptable for inclusion for two or more of the following reasons: lack of maternal consent, birth complication, family not English-speaking, and location of residence. Each child was counted only once, according to the first of these reasons. Therefore, except for "lack of maternal consent," the numbers in the table understate the incidence of the various reasons for exclusion.

†Complications included Down's syndrome, retinoblastoma, cleft palate, gestational age  $<34$  weeks, and others.

‡Subjects were excluded if they lived  $>19$  km from Boston, or in an area considered unsafe for home visitors.

§Mothers had two opportunities to refuse to participate. While still in the hospital, all the mothers were asked for permission to be contacted in the future about participating in a follow-up study. Some refused this request; some who gave consent at this time refused when subsequently contacted.

three significant figures by isotope-dilution mass spectrophotometry, were included after they became available from the Centers for Disease Control in 1982. Further details about the blood lead measurements are available elsewhere.<sup>23</sup>

In the sample as a whole, the mean blood lead level was  $<8 \mu\text{g}$  per deciliter at all the ages sampled. The differences in exposure level among the three cord-blood groups did not carry over into the postnatal period (Table 3). Although the mean postnatal lead levels of infants in the high cord-lead group exceeded those of infants in the low cord-lead group at all ages, the difference was statistically significant only at 12 months. The means of the infants in the medium and high cord-lead groups did not differ significantly at any postnatal age. Most important, the correlation between cord and postnatal blood lead level did not exceed 0.20 at any age.<sup>24</sup> The equality of postnatal exposures in groups with widely discrepant prenatal exposures provided us the opportunity to assess the developmental effect of prenatal exposure in the absence of substantial confounding by postnatal exposure.

### Sample Attrition

Forty-five infants were lost to follow-up at some point in the study — an attrition rate of approximately 10 percent per year. The likelihood of loss increased slightly with decreasing lead levels in umbilical-cord blood ( $\chi^2 = 1.22$ ;  $P > 0.50$ ). The percentage of infants who did not complete all visits was 21.2, 18.2, and 14.5 percent for the low, medium, and high cord-lead groups, respectively. As compared with the mothers of the infants who remained in this study, the mothers who withdrew their children were more likely to be nonwhite or unmarried, and their mean age, educational level, IQ, and socioeconomic status were lower. They also had lower scores on a measure of the quality of the rearing environment they provided for their six-month-old infants.<sup>25</sup>

### Cases Excluded from Analyses

Seven sets of twins enrolled in the study were not included in the statistical analyses because of their generally poorer performance relative to the nontwins in the sample. Earlier analyses of Mental Development Index scores at six months of age showed that restricting the sample to nontwins did not affect the results appreciably.<sup>10</sup> Another four infants were excluded because of the diagnosis of a serious medical condition known to be associated with developmental handicap (congenital heart defect, prenatal toxoplasmosis infection, myoclonic seizure disorder, and severe hypotonia).

The statistical analysis is described in the Appendix.

## RESULTS

### Exploratory Analyses

Infants who had higher lead levels in umbilical-cord blood had lower crude Mental Development Index scores during the first two years of life. This relation was stronger when the 12 potential confounders were taken into account (Table 4). Despite a steady increase with age in the scores of infants in all three exposure groups, the least-

squares mean Mental Development Index scores of the infants in the high cord-lead group were 4 to 8 points lower than those of the infants in the low cord-lead group at all ages (Fig. 1). The mean scores of the infants in the low and medium groups were similar throughout this age range.

The pattern of the adjusted Mental Development Index (MDIA) scores illustrates the consistency in the direction and magnitude of the relation between Mental Development Index and prenatal lead exposure (Table 5). A plus or minus sign indicates whether, on average, the infants within a group did better (+) or worse (−) than predicted at a given age on the basis of the 12 variables considered potential confounders. The average MDIA was increasingly negative with increasing prenatal exposure. The infants in the low cord-lead group averaged  $1.9 \pm 0.4$  points, those in the medium cord-lead group  $1.2 \pm 0.8$ , and those in the high cord-lead group  $-3.4 \pm 1.1$ . The

Table 2. Characteristics of Families in the Three Cord-Blood Lead Groups.\*

CHARACTERISTIC	CORD-BLOOD LEAD GROUP†			P VALUE‡
	LOW	MEDIUM	HIGH	
<b>Demographic</b>				
Marital status (% single)	17.3	7.2	10.8	0.13
Maternal age (yr)	28.2±4.6	30.0±4.8	30.9±5.1	0.002
Race (% white)	79.0	95.2	85.1	0.015
Maternal education§	16.0±3.8	16.5±3.9	16.3±4.1	0.76
Prenatal education§	17.3±3.5	18.0±3.6	17.7±3.6	0.51
Family social class§	2.3±1.7	2.2±1.8	2.3±2.0	0.94
<b>Reproductive history¶</b>				
Gravidity	2.3±1.2	2.1±1.6	2.3±2.0	0.57
Parity	0.6±0.5	0.5±0.5	0.4±0.5	0.14
Miscarriage (% with any)	18.5	10.8	24.3	0.08
<b>Index pregnancy</b>				
Month prenatal care began	2.5±1.0	2.2±0.9	2.1±0.7	0.021
Length of gestation (wk)	39.6±1.8	40.1±1.6	40.0±2.0	0.14
Weight gain (lb)	31.5±10.7	32.0±11.4	28.3±9.8	0.063
Hypertension (%)	11.1	8.4	12.3	0.72
Bleeding (%)	7.4	9.6	4.0	0.40
Cigarette smoking (%)	21.0	34.9	28.4	0.14
Smoking duration (yr)	2.2±3.6	5.2±5.8	6.7±6.6	0.0001
Alcohol consumption (%)**	25.9	41.0	50.0	0.008
<b>Labor and delivery¶</b>				
Duration of stage 1 (hr)	8.6±6.8	7.9±4.6	8.3±4.9	0.89
Vaginal delivery (%)	77.5	78.0	71.6	0.59
No or local anesthesia (%)	40.3	24.4	35.2	0.10
<b>Neonatal status</b>				
Birth weight (g)¶	3316±474	3478±521	3379±538	0.12
Apgar score: 5 min¶	8.9±0.6	8.8±0.5	8.8±0.5	0.60
Sex (% male)	59.3	56.6	50.0	0.49
<b>Postnatal environment</b>				
H.O.M.E. total score††				
6 Mo	34.4±3.8	35.1±3.5	35.3±3.4	0.33
24 Mo	36.8±3.2	37.2±3.0	37.0±3.1	0.76
Mother's IQ‡‡	119.0±20.9	123.3±17.1	121.7±18.4	0.38

\*For dichotomous variables, differences between groups were evaluated by overall chi-square tests. For continuous variables, group differences were tested by one-way analyses of variance.

†Plus-minus values are means ±SD.

‡Indicates P value associated with the hypothesis that differences among infants in the three cord-blood lead groups were due to chance.

§Weighted scores were computed with use of Hollingshead's Four-Factor Index of Social Status.

¶The information was obtained from obstetrical or pediatric records; otherwise, it was obtained in an interview with the mother.

||Values are the percentages of women who reported smoking during any portion of the index pregnancy.

\*\*Values are the percentages of women who reported having consumed, on average, one or more drinks per week during the third trimester of the index pregnancy.

††H.O.M.E. denotes Home Observation for the Measurement of the Environment.

‡‡The mother's IQ was measured with the Peabody Picture Vocabulary Test.

number of positive MDIA scores was determined for each infant. This corresponds to the number of ages at which the infant had a Mental Development Index score that exceeded the predicted value. The percentage of infants who did not score higher than predicted at any of the four ages was three times higher in the high cord-lead group than in the low or medium groups (23.6 percent vs. 8.5 and 6.5 percent, respectively).

Infants' Mental Development Index scores were not associated with their prior postnatal or concurrent blood lead levels.

### Longitudinal Analyses

In all the longitudinal models fitted, the lead variables most strongly associated with MDIA scores were those that compared the overall level of performance of infants in the low and high cord-lead groups or the medium and high cord-lead groups. The estimated deficit in the overall MDIA score of infants in the high cord-lead group was 4.8 points (95 percent confidence interval, 2.3 to 7.3;  $P = 0.0001$ ) with respect to the infants in the low group, and 3.8 points (95 percent confidence interval, 1.3 to 6.3;  $P = 0.004$ ) with respect to infants in the medium group.

Age trends in MDIA scores were not significantly related to cord-lead group (Model 2) or to early postnatal lead exposure (Model 5). Similarly, MDIA scores were not related significantly to the blood lead concentration at the time of developmental assessment (Model 3) or to cumulative postnatal lead exposure up to the time of assessment (Model 4). (Additional details about the models and their relative fit are available from the authors.)

### DISCUSSION

Infants with lead levels in umbilical-cord blood of 10 to 25  $\mu\text{g}$  per deciliter — levels currently considered acceptable — had stable performance deficits of 0.25 to 0.5 SD during the first two years of life, relative to infants with levels under 10  $\mu\text{g}$  per deciliter. Postnatal blood lead levels of comparable magnitude, measured during the first two years of life, were not associated with performance deficits.

This association between development and prenatal lead exposure but not between development and post-

Table 4. Infants' Mental Development Index Scores According to Cord-Blood Lead Group.

CORD-BLOOD LEAD GROUP	MENTAL DEVELOPMENT INDEX SCORE			
	6 MO	12 MO	18 MO	24 MO
	mean $\pm$ SD			
Crude score				
Low	109.2 $\pm$ 12.9	113.1 $\pm$ 12.5	113.4 $\pm$ 15.5	115.9 $\pm$ 17.2
Medium	108.6 $\pm$ 12.0	115.4 $\pm$ 12.9	116.6 $\pm$ 16.7	119.9 $\pm$ 14.4
High	106.1 $\pm$ 11.1	108.7 $\pm$ 12.8	109.5 $\pm$ 17.5	110.6 $\pm$ 16.5
	mean $\pm$ SE			
Controlled for potential confounders*				
Low	110.2 $\pm$ 1.3	114.7 $\pm$ 1.6	116.2 $\pm$ 1.9	118.9 $\pm$ 1.8
Medium	108.0 $\pm$ 1.3	114.4 $\pm$ 1.5	114.8 $\pm$ 1.9	117.8 $\pm$ 1.7
High	105.9 $\pm$ 1.4	108.9 $\pm$ 1.6	109.5 $\pm$ 2.0	111.1 $\pm$ 1.8
P value†	0.095	0.020	0.049	0.006
No. of infants‡	201	199	187	182

\*Least-squares mean  $\pm$  SE, derived from regression equations that included 12 potential confounders (see text) and cord-blood lead group coded as two indicator variables.

†Indicates P value associated with the F ratio that evaluates whether the mean Mental Development Index for any cord-blood lead group differed significantly from the common mean after potential confounders were controlled for.

‡The numbers of infants at the four ages differ from one another and from those shown in Table 1 because of (1) loss to follow-up between Mental Development Index assessments and (2) the exclusion from the analyses of twins, infants with handicapping medical conditions, and infants for whom the Mental Development Index or confounder values were unavailable.

natal lead exposure may be interpreted in one of three ways. First, it may have been an artifact of study design. We selected for extremes of prenatal lead exposure but not for extremes of postnatal lead exposure. The mean lead level in the cord blood of the infants in the high group exceeded the mean level of the infants in the low group by a factor of 8, whereas the mean postnatal blood levels of lead in the two groups were much more comparable, never differing by more than 3  $\mu\text{g}$  per deciliter. Although this design allowed us to appreciate an association between development and prenatal lead exposure, it may have limited our ability to perceive a small postnatal effect.

Second, early postnatal exposure corresponding to blood lead levels in the upper portion of the range from 0 to 25  $\mu\text{g}$  per deciliter may not adversely affect infants' performances on the Bayley Scales.<sup>26</sup>

Third, adverse effects associated with postnatal exposures in this range may be discernible only at later ages or in infants who are at greater risk of poor outcome on the basis of socioenvironmental factors than those in our sample.

The performance deficits we observed were consistent with studies in primates in which learning deficits produced by the prenatal or early postnatal administration of lead persisted in some cases for several years after the blood lead levels of the exposed animals fell to the control level.<sup>27-32</sup> This may be attributable to the fact that brain lead levels remain elevated considerably longer after a short-term exposure than do blood lead levels.<sup>33,34</sup>

Like malnutrition and other developmental insults, lead's adverse effects may be expressed most dramatically when exposure occurs in conjunction with other factors that compromise a child's development. In-

Table 3. Blood Lead Levels in Infants Classified According to Cord-Blood Lead Group.

CORD-BLOOD LEAD GROUP	BLOOD LEAD LEVEL (MEAN $\pm$ SD)				
	BIRTH*	6 MO	12 MO†	18 MO	24 MO
	micrograms per deciliter				
Low	1.8 $\pm$ 0.6	4.6 $\pm$ 3.9	5.8 $\pm$ 5.1	6.7 $\pm$ 5.5	5.4 $\pm$ 4.8
Medium	6.5 $\pm$ 0.3	7.0 $\pm$ 7.8	8.5 $\pm$ 7.6	8.3 $\pm$ 5.8	7.2 $\pm$ 5.0
High	14.6 $\pm$ 3.0	7.0 $\pm$ 8.7	8.8 $\pm$ 6.4	7.6 $\pm$ 5.8	7.7 $\pm$ 8.5

\*Each value is significantly different from the other two (Tukey's studentized range test;  $\alpha = 0.05$ ).

†The value for the low-lead group is significantly different from the other two values (Tukey's studentized range test;  $\alpha = 0.05$ ).

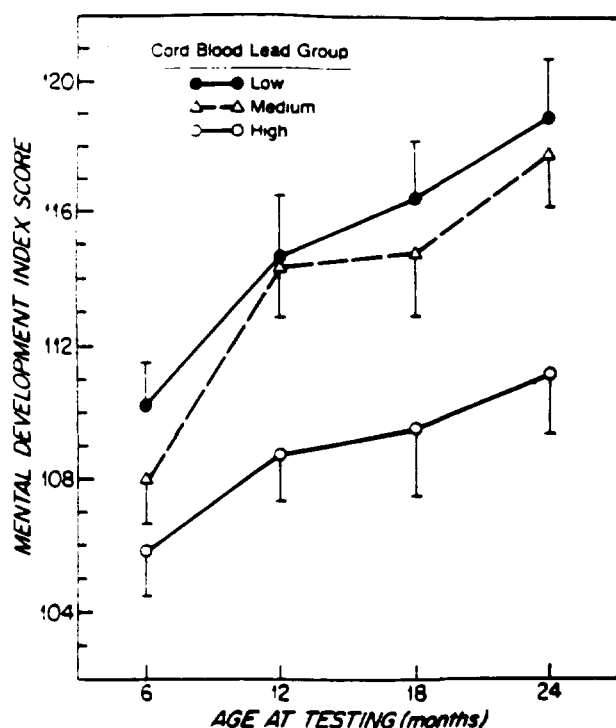


Figure 1. Mean Mental Development Index Scores at Four Ages in Infants According to the Lead Level in Umbilical-Cord Blood. Scores are least-squares means obtained by regressing Mental Development Index scores on the cord-blood lead group and 12 variables considered to be potential confounders. Error bars represent 1 SD. For clarity, bars extend only in one direction.

deed, in a German study of school-aged children, visual-motor integration and reaction-time performance were adversely affected only among the children exposed to lead who were also socially disadvantaged.<sup>35</sup> If this is also true for prenatal lead exposure and early infant development, our sample provides a conservative assessment of the association. The early results of another longitudinal study of the developmental effect of prenatal lead exposure, conducted in a less socially advantaged sample, support this interpretation.<sup>36</sup>

Our sample, a relatively homogeneous group of families willing to contribute substantial time and effort to participate in longitudinal research, cannot be considered representative of the population of U.S. infants. The increasingly high Mental Development Index scores over the 6- to 24-month period of infants in all the exposure groups are most likely due to the overrepresentation in this sample of infants from families in the higher socioeconomic strata. In addition, the mean blood lead level of the sample as a whole never exceeded half the mean level of U.S. preschool children,<sup>1</sup> and infants with serious handicaps or characteristics strongly associated with handicap were excluded from the sample. In addition, infants were not sampled in such a way that the distribution of levels of cord-blood lead matched the distribution in all infants.

Some of the design features of our study would be expected to reduce the likelihood that an effect of prenatal lead exposure would be perceived. Indeed, the association did not become significant until after adjustment for potential confounders. Moreover, the estimate of the prenatal effect became larger and its significance level more extreme the greater the number of potential confounders included in the regression equation.<sup>37</sup> This finding is unique among lead studies and can be attributed to the fact that the more socioeconomically advantaged infants in our sample tended to have higher levels of lead in umbilical-cord blood.<sup>38</sup> On the basis of a regression equation consisting of the 12 potential confounders, the predicted Mental Development Index scores of the infants in the high cord-lead group were higher than the predicted scores of the infants in the low cord-lead group at all four ages. As a result, adjusting for these variables enhanced rather than reduced the estimate of lead's association with Mental Development Index scores.

The adequacy of the lead level in umbilical-cord blood as an indicator of intrauterine lead exposure has not been studied in detail. The lead level in cord blood is strongly correlated with the concurrent lead level in the mother's venous blood.<sup>39-42</sup> The mother's lead level appears either to remain stable or to decline slightly over the course of pregnancy.<sup>40,41,43,44</sup> Nevertheless, we advise caution in extrapolating the lead exposure throughout pregnancy from just one blood measurement at the time of delivery.

The pattern of attrition in this study provides a striking example of the bias that can occur when loss to follow-up is related to the exposure or the outcome of interest and the statistical approach employed uses only subjects for whom complete data are available. Although the overall rate of attrition did not vary significantly among the prenatal-exposure groups, the relation between loss to follow-up and development did. The infants in the low cord-lead group who did not complete the study tended to have more improvement in performance over the period of their participation than did the infants in the low group who remained in the study. Those in the high cord-lead

Table 5. Infants' Mean Adjusted Mental Development Index Scores (MDIA) According to Cord-Blood Lead Group.\*

Cord-Blood Lead Group	MDIA Scores			
	6 MO	12 MO	18 MO	24 MO
Low				
Mean score $\pm$ SE	1.72 $\pm$ 1.20	1.46 $\pm$ 1.46	2.12 $\pm$ 1.75	2.28 $\pm$ 1.58
No. of infants†	70	69	65	61
Medium				
Mean score $\pm$ SE	-0.06 $\pm$ 1.25	1.60 $\pm$ 1.38	1.22 $\pm$ 1.76	1.82 $\pm$ 1.60
No. of infants†	70	70	65	63
High				
Mean score $\pm$ SE	-1.90 $\pm$ 1.21	-3.54 $\pm$ 1.54	-3.81 $\pm$ 1.97	-4.38 $\pm$ 1.76
No. of infants†	61	60	57	58

\*The MDIA score is the residual of the regression of Mental Development Index on the 12 variables considered potential confounders; MDIA scores are the dependent variables in the longitudinal analyses.

†Values are the numbers of infants for whom MDIA scores were available.

group who did not complete the study tended to have a greater decline in performance over the period of their participation than did the infants in the high group who remained in the study. Basing the longitudinal-modeling analyses only on the infants for whom Mental Development Index scores were available at all four ages would have biased the result toward underestimation of the relation between prenatal lead exposure and development.<sup>15,46</sup>

Recent estimates of lead levels in umbilical-cord blood in subjects in urban areas are typically 7 to 9  $\mu\text{g}$  per deciliter, with an SD of 3 to 4.<sup>15,39,47-50</sup> Thus, more than one fourth of all newborns in these areas may have lead levels comparable to those of the infants in our high-exposure group (i.e.,  $\geq 10 \mu\text{g}$  per deciliter). If replicated in other samples, our findings suggest that the current standard of the Centers for Disease Control for acceptable blood lead levels in young children ( $< 25 \mu\text{g}$  per deciliter) should not be applied to fetuses.

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## APPENDIX: STATISTICAL METHODS

Data analyses were conducted in two stages. First, the associations between the various lead measures and Mental Development Index scores were examined separately for each age. The goal was to suggest hypotheses to investigate in the second stage. These exploratory analyses consisted of ordinary least-squares multiple regressions in which Mental Development Index scores were regressed on the cord-blood lead category and a set of 12 factors generally associated with infant development: the mother's age, race (white or nonwhite), IQ,<sup>31</sup> education, number of years of cigarette smoking, and number of alcoholic drinks per week in the third trimester of pregnancy; the mean family social class over the period of the study (according to the Hollingshead Four-Factor Index); the quality of the care-giving environment<sup>25</sup>; and the infant's sex, birth weight, gestational age, and birth order.

In the second stage, longitudinal analyses were carried out with use of weighted regression.<sup>32</sup> This was considered more appropriate than ordinary least-squares regression, because it takes into account the correlation between an infant's Mental Development Index scores at different ages. In these analyses, adjustment for potential confounders preceded evaluation of lead's contributions to Mental Development Index scores. The dependent variables — the adjusted Mental Development Index (MDIA) scores — are the residuals of the regression of Mental Development Index scores on the 12 potential confounders listed above. Because the relation between a potential confounder and infant performance may change with time, Mental Development Index scores were adjusted in four separate regression analyses, one for each age. In both exploratory and longitudinal analyses, the cord-lead group was represented as two indicator variables, with the high group as the reference group. Postnatal blood lead levels, transformed to their natural logarithms, were treated as continuous variables.

Five models were fitted, each postulating specific relations between MDIA and lead exposure during different periods. These

models were chosen to assess the effect of prenatal and postnatal lead exposure on the overall level of performance and rate of change in the MDIA score. All five included a term relating prenatal exposure (cord-lead group) to the mean MDIA score. The simplest model (Model 1) considered no other influences. Other models included terms representing more complex relations. Model 2, prenatal lead exposure affects the temporal change in MDIA score; Model 3, blood lead level at the time of assessment affects the MDIA score; Model 4, cumulative lead exposure up to the time of assessment affects the MDIA score; and Model 5, the blood lead level at the age of six months interacts with the cord-lead group to affect a subsequent temporal change in the MDIA score.

In all the models, MDIA scores for an individual child at the  $i$ th visit were expressed as the sum of the mean  $\mu_i$  and a random component  $e_i$ :

$$\text{MDIA}_i = \mu_i + e_i$$

where the  $e_i$ s for a child have a multivariate normal distribution, with a mean of 0 and an arbitrary covariance matrix  $\Sigma$ , assumed to be the same for all children for whom data were complete (i.e., MDIA scores were available for each age). For children with incomplete data, the appropriate rows and columns were deleted from the covariance matrix.

The covariance matrix was estimated from the data with use of an iterative algorithm. In a first step,  $\Sigma$  was estimated by computing the sample covariance matrix of the residuals of the ordinary (unweighted) least-squares estimate of the regression of the MDIA score against the lead-exposure variables. The inverse of the estimated  $\Sigma$  provided the weights given to the observations made in a child. These were then used to compute the weighted least-squares estimates of the coefficients and their standard errors.

Parallel analyses were conducted in which two features of the method were varied. In one set (Waternaux C, Laird NM, Ware JH: unpublished data), adjustment was made for potential confounders selected empirically (viz., those determined to be responsible for any differences between crude and adjusted estimates of lead's association with Mental Development Index scores).<sup>38</sup> In the other set, unadjusted Mental Development Index scores were subjected to regression, in a one-stage analysis, on the 12 confounders and the lead terms specified in the various models. These alternative approaches produced results equivalent to those obtained in the two-stage analysis that involved adjustment for the 12 confounders listed above. Only the results of the latter sets of analyses are presented.

The algorithm for iterative weighted least-squares regression was programmed with use of the Statistical Analysis System.<sup>33</sup> All  $P$  values are two-tailed.

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